A Case of Stage IV Gastric Cancer: Long-term remission achieved with S-1 mono-chemotherapy

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Abstract

S-1 is a recently developed agent that reduces the gastrointestinal toxicity of 5-fluorouracil without affecting its antitumor activity. We encountered a patient with advanced gastric cancer, who responded to S-1 mono-chemotherapy and has maintained complete remission for over 4 years. The case was of a 61-year-old man who presented with abdominal pain in July 2001 and was diagnosed with stage IV gastric cancer (T4N2M0). Curative surgery such as gastrectomy was not appropriate, and mono-chemotherapy with S-1 was administered. This was given for 4 consecutive weeks at a dose of 120 mg/day, followed by a 2-week rest period; 18 courses were administered until September 2003. These cases suggest that a subgroup of patients with advanced gastric cancer may attain a complete response with S-1 chemotherapy, with or without gastrectomy.

Key words Stomach neoplasms, Drug therapy, TS-1, S-1

Introduction

S-1 is a drug containing three components, tegafur, an oral anticancer agent that is a prodrug of 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxy-pyridine (CDHP), and monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate (Oxo).1–3 This combination reduces the gastrointestinal toxicity of 5-FU without affecting its antitumor activity.1–3 The safety of S-1 and maximum tolerable dose has been determined through phase I clinical trials.4–11 Moreover, the efficacy of S-1 as mono-chemotherapy12–14 or in combination with cisplatin15–17 against advanced gastric cancer has been measured through phase II clinical trials. However, although the response rate was 20–50%, patients rarely attain a complete response to S-1 mono-chemotherapy.12–14 In addition, the median survival time and 1-year survival rates of patients with advanced gastric cancer treated with S-1 are 6 to 12 months and 33 to 36%, respectively.18–20 We encountered a patient with advanced gastric cancer, who was administered S-1 mono-chemotherapy at home as a palliative treatment. Against our prediction, the patient responded completely to S-1 and has maintained remission for more than 4 years after starting chemotherapy.

Case

A 61-year-old man presented with abdominal pain on July 19, 2001. Upper gastrointestinal series (Fig. 1A; upper panel) and endoscopy
Before chemotherapy (July 2001)

(Fig. 1B; upper panel) demonstrated an ulcerative lesion extending along the lesser curvature of the stomach from the cardia to the pyloric region. Examination of a biopsy specimen showed adenocarcinoma with undifferentiated histology. Moreover, abdominal computed tomography (CT) suggested direct invasion of cancer to the pancreatic body, lymph node metastases (mainly on the lesser curvature side of the gastroesophageal junction), as well as diffuse invasion of the gastric wall (Fig. 1C; upper panel). Laparotomy performed on July 30 2001 confirmed the following findings: 1) tumor invasion extending out of the stomach wall and adjacent to both the great omentum and lesser omentum; 2) direct invasion into the pancreas; 3) enlarged lymph nodes at multiple sites; and 4) class II cells in ascetic fluid. The patient was accordingly diagnosed as having stage IV (T4, more than N2M0) gastric cancer. Hence, curative therapy including gastrectomy was not considered beneficial for this patient, and the only surgical intervention performed was

the construction of a button-type jejunal fistula at approximately 20 cm anal to the Treitz’ ligament to support enteral nutrition.

Mono-chemotherapy with S-1 was started from August 12, 2001. One course consisted of S-1 (TS-1®, Taiho Pharmaceutical Co., Ltd, Saitama, Japan) for 4 consecutive weeks at a dose of 120mg/day, followed by a 2-week rest period. A total of 18 courses was administered until September 10, 2003. After the first two courses of S-1, the gastric wall appeared thinner, lesser curvature lymphadenopathy had reduced, and the pancreatic lesion had been replaced by fat tissue (Fig. 1C, lower panel). Upper gastrointestinal endoscopy performed on December 12, 2001, after four courses of S-1, revealed

Before chemotherapy (July 2001)

After chemotherapy (March 2005)

After chemotherapy (December 2001)

Recent (June 2005)

Fig. 1A Upper gastrointestinal series
Arrows present existence of tumor.

Fig. 1B Upper gastric endoscopy
Arrows present existence of tumor.
remarkable shrinkage of the lesser curvature tumor. Moreover, its appearance had changed to resemble an H2 stage gastric ulcer (Fig. 1B, middle panel). Cancer cells were not detected in biopsy specimens from plausible lesions. Therefore, the patient was considered to have achieved a complete response after 4 courses of S-1 mono-chemotherapy, without either gastrectomy or radiotherapy. After completion of the 18th course of S-1 treatment on September 11, 2003, the patient has remained in good health without any anticancer therapy. No sign of recurrence has been noted on upper gastrointestinal endoscopy with biopsy repeated every four months for nearly 2 years. Serum levels of CEA and CA 19-9 remained within normal limits before and after the chemotherapy. Recent findings with upper gastrointestinal series (Fig. 1A; lower panel) and endoscopy (Fig. 1B; lower panel) are also shown.

During 18 courses of S-1, all adverse events (which included pigmentation of the skin and nails) were minor and classified as grade I. The patient remains in complete remission as of September 26, 2005.

Discussion

We have reported a patient with advanced gastric cancer who responded well to S-1 mono-chemotherapy and has maintained complete remission for 4 years after starting treatment. Since S-1 was released on the Japanese market in 1999, many case reports have demonstrated the marked effectiveness of this drug on advanced gastric cancer, similar to that observed in the present two cases. However, this seems to contrast with response patterns shown by phase II clinical trials. Phase III clinical trials comparing the effectiveness of S-1 with continuous 5-FU infusion as the reference arm have not yet reached a final conclusion, and it hence remains unknown whether S-1 is superior to 5-FU in terms of survival of patients with advanced gastric cancer. However, S-1 may induce a complete response in a certain subgroup of patients with advanced gastric cancer. The treatment effects of S-1 mono-chemotherapy for gastric cancer can be determined by the status of thymidylate synthase gene expression. In lung cancer, specific single poly-
morphism have been demonstrated to predict responses to gefitinib.\(^{47,48}\) Exploring such molecular markers to predict a complete response to S-1 may a clinically beneficial future direction.

Eighteen courses of S-1 for the patient could be administered at home, without disrupting the patient’s occupational routine. To overcome anorexia after starting S-1, we concurrently administered enteral nutrition through a jejunal fistula created at operation. We believe this device enables us to continue S-1 chemotherapy at home as long as possible and results in maximum tumor shrinkage.

In conclusion, we encountered a patient with advanced gastric cancer who exhibited a complete response to S-1 mono-chemotherapy and has maintained remission for more than 4 years after starting treatment.

References

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